What is the Value of Total Mesopancreas Excision in Pancreatic Ductal Adenocarcinoma? Current Evidence of the Literature

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Rezumat

Care este valoarea exciziei complete a mezopancreasului în carcinomul ductal pancreatic? Analiza datelor din literatură

Carcinomul ductal pancreatic (PDAC) este o afecțiune cu prognostic infaust. Rezecția pancreatică reprezintă singura șansă de supraviețuire pe termen lung în cazul unui pacient diagnosticat cu PDAC. Recidiva după chirurgia cu viză curativă pentru PDAC este frecventă și se datorează în cea mai mare parte marginilor de rezecție pozitive: marginea medială/ de la nivelul arterei mezenterice superioare cel mai frecvent. Excizia completă a mezopancreasului (TMpE) a fost propusă în analogie cu excizia totală a mezorectului în cancerul rectal, pentru un mai bun control al recidivei loco-regionale. Lucrarea își propune să discute datele existente la momentul actual în literatura de specialitate privind valoarea TMpE în PDAC.

Cuvinte cheie: carcinom ductal pancreatic, pancreatectomie, mezopancreas, excizie completă de mezopancreas, recidivă, supraviețuire

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a disease with a grim prognosis. Pancreatectomy represents the single hope for long-term survival in a patient with PDAC. Recurrence is a common event after curative-intent surgery for PDAC, mainly related to incomplete removal at the site of resection margins; medial/ superior mesenteric margins are the most often positive. The concept of total meso-

Received: 21.11.2017
Accepted: 17.12.2017

pancreas excision (TMpE) in PDAC was proposed in analogy to the concept of total mesorectal excision for rectal cancer, to better control loco-regional recurrence. This paper aims to discuss the current evidence for the value of TMpE in PDAC.

Key words: pancreatic ductal adenocarcinoma, pancreatectomy, mesopancreas, total mesopancreas excision, recurrence, survival

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains in 2017 an important cause of death by cancer both in the United States and Europe (1,2). More than 80% of patients with PDAC have locally advanced and/or metastatic disease at the time of diagnosis (2). Thus, the prognosis of most patients diagnosed with PDAC is grim, with a 5-year survival rate of 8% for all stages (2).

Pancreatectomies represent the single hope for a long-term survival in a patient with PDAC but are possible in less than 20% of the patients (2). A study performed in the United States based on data from Surveillance, Epidemiology, and End Results registry has shown that a pancreatectomy is associated with statistically significant increased survivals for patients with resectable PDAC (i.e., stage I/ II), compared with any other form of therapy (3). Furthermore, a recent study performed in the Netherlands has shown that the percentage of patients with PDAC who survived more than 5 years is significantly higher after resection (10.1%), compared with patients with unresected localized or metastatic disease (0.5% and 0.1%, respectively)(4). Median overall survival time after resection for PDAC is approximately two years (5-8).

In patients with resectable PDAC, the prognosis is driven mainly by tumor-related factors (i.e., tumor diameter, differentiation grade, lymph node status and ratio, and involvement of surgical margins) and completion of adjuvant therapy (9). Thus, one might question what could be the contribution of a surgeon to better prognosis in a patient with PDAC?

Increased resectability and reduced post-operative mortality rates are the main contributions of a surgeon to better prognosis in a patient diagnosed with PDAC and are feasible if patients are operated in high-volume centers by high case-load surgeons (10-13).

In the last years, although several signs of progress have been observed in adjuvant therapy for PDAC (14), these advances in developing effective treatments are by far too modest. At the same time, several potential improvements were proposed to better resect PDAC, including total mesopancreas excision (TMpE) (15).

Initially, a systematic review of the literature performed in 2008 did not show any significant improvements for overall survivals after resection for PDAC (6). However, a study published in 2017 including 15 604 patients with pancreatectomies for PDAC has shown that median survival time has significantly increased from 14 months between 1992 – 1997 to 18 months between 2004 – 2010 (16).

This paper aims to discuss the current evidence for the value of TMpE in PDAC. It is worth to mention that in the literature there are used the following terms: total mesopancreas (meso-pancreas) excision(15,17-20) and total meso-pancreatoduodenum excision (21,22).

What are the recurrence rates and resection margins status after curative-intent surgery for PDAC?

Recurrence after curative-intent surgery for PDAC is unfortunately a common event – 75% - 100% of patients(15,23-25); a local recurrence is the first reported event for most patients with recurrent PDAC(7;26). Incomplete lymph

nodes or perineural dissection are considered factors associated with local recurrence after resection for PDAC (23). Furthermore, local recurrence occurs more frequently in patients with positive resection margins (26). Thus, negative resection margins operative specimen is of utmost importance in patients with resected PDAC (15).

Negative resection margins rates reported in the literature recognize a large variability, due to different definitions and techniques for assessment (26), mainly related to pathological evaluation (27).

In a meta-analysis performed in 2008, the reported incidence of positive resection margins after curative-intent surgery for PDAC was up to 32% of patients, with no impact on long-term outcomes (28). However, for these patients no standardized pathology protocol was used (28).

Standardization of protocol for pathological examination has lead to increased reported positive resection margins rates after pancreaticoduodenectomies (PD) for PDAC: 71% - 84.6% (29-34).

Recent systematic review and meta-analyses have noticed that overall incidence of negative resection margins ranged between 8.1% and 84% (26,35,36). The medial/ superior mesenteric artery margin was the most often positive, ranging between 15% and 45% (26,35). Studies concluded that positive resection margins have a detrimental effect on long-term outcome after resection for PDAC (26,35,36), and the inability to clear the medial/superior mesenteric artery margin represents the most important cause of incomplete resection (26,35).

A recent study performed in Heidelberg has shown that positive resections margins are associated with significantly decreased overall survival and recurrence-free rates (7). Thus, median overall survival time and recurrence-free rate in patients with negative resections margins were significantly higher, compared with patients with positive margins (24.9 months vs. 18.7 months and 15.7 months vs. 11.9 months, respectively)(7). Positive resections margins were by far more frequently

observed to the medial margins (7).

The use of standardized pathological protocol to assess margins after resection for PDAC has shown that overall survival rates are significantly different between positive and negative resection margins patients (10.5 - 23.4 months vs. 18.9 - 41.6 months) (29,31-34).

Positive resection at the medial/ superior mesenteric margins is widely considered to have a significant impact on both recurrence and overall survival rates in PDAC (24,31). A study published in 2010 has shown that overall survival time in patients with positive transection margins (including medial/superior mesenteric margins) is significantly worse, compared with patients with positive mobilization margins (31).

In conclusion, a recurrence is a common event after curative-intent surgery for PDAC, mainly related to incomplete removal at the site of resection margins. Although negative resection margins are the main goal of curative-intent surgery for PDAC and were associated with improved survivals, however, positive resection margins rates are highly reported after pancreatectomies for PDAC, even in high-volume centers, when standardized pathology protocols are used. Medial/ superior mesenteric margins are the most often positive, with a detrimental effect on both recurrence and overall survival rates in PDAC.

What is the mesopancreas and what is the technique of TMpE?

The concept of TMpE in PDAC was proposed in analogy to the concept of total mesorectal excision for rectal cancer, to better control loco-regional recurrence (23,37).

As already shown, loco-regional recurrence is a frequent event after curative-intent surgery for PDAC and appears to be related with high incidence of tumor invasion and high positive resection margins rates at medial/superior mesenteric artery margins (23). A local recurrence is widely considered to be generated by incomplete removal at the site of resection (38). Thus, a technique to better resect the retro-

pancreatic area would be of interest and another potential contribution of pancreatic surgeons to improved outcomes in PDAC.

It is the merit of Goekel and co-workers (37) to introduce the concept of TMpE in PDAC, a concept that recognized furthermore a great interest, is considered a promising surgical technique for patients with PDAC (39).

Goekel and co-workers described for the first time the mesopancreas as firm and well-vascularized structure (perineural lymphatic layer) extending from posterior surface of the pancreatic head to behind the superior mesenteric vessels (37). En-bloc resection of this structure during PD for PDAC was suggested, following a perineural plane (37).

Several other anatomical studies have shown that the structure namely considered mesopancreas contain loose connective tissues, fat, lymph nodes, lymphatic and nerves, along with small blood vessels, but there is no fascia of fibrous layer to cover the mesopancreas, as it is the case for mesorectum (40,41) (*Fig. 1*). Thus, a dissection plane for TMpE does not appear to exist to allow en-bloc resection (40); however, instead, subadventitial dissection of superior mesenteric artery is suggested to resect the mesopancreas (41).

Some authors consider the mesopancreas as soft connective tissue situated along the inferior pancreaticoduodenal artery and first jejunal

Figure 1. Operative specimen of pancreatico-duodenectomy for pancreatic head ductal adenocarcinoma (PH – pancreatic head; Mp – mesopancreas)

artery, and developed surgical techniques to resect the mesopancreas guided by the course of these arteries (21,22) (*Fig. 2* and *3*).

Nevertheless, there are also authors that consider mesopancreas a misnomer because it does not include all the blood supply and lymphatic networks of the pancreatic head (42). The term suggested to replace mesopancreas is pancreatic head plexus II (nerve tissue distributed to uncinate process from superior mesenteric artery plexus, including inferior pancreaticoduodenal artery), as Japan Pancreas Society recently proposed (42,43). Other terms used in the literature to describe

Figure 2. Preoperative assessment of a pancreatic head ductal adenocarcinoma (T) by contrast enhanced computed tomography (A) coronal plane and (B) frontal plane to guide pancreatico-duodenectomy with total mesopancreas excision by inferior pancreaticoduodenal artery (* and arrow marks the inferior pancreaticoduodenal artery; SMA – superior mesenteric artery; SMV – superior mesenteric vein; the line marks the plane for transection).

Figure 3. Intraoperative aspects of pancreaticoduodenectomy with total mesopancreas excision guided by inferior pancreaticoduodenal artery (IPDA – inferior pancreaticoduodenal artery; SMA – superior mesenteric artery; SMV – superior mesenteric vein; PV – portal vein; CBD – common bile duct; PH – pancreatic head; Mp – mesopancreas)

the structure of mesopancreas are retroportal lamina or retroportal pancreas (23).

Gaedcke and co-workers analyzing the operative specimens of PD for periaampullary malignancies observed tumor infiltration of mesopancreas in approximately two-thirds of

patients with positive resection margins (38). Thus, the authors concluded that mesopancreas is the primary site for positive resection margins (38).

We have previously emphasized the key role of TMpE in PDAC (15). However, it is the merit of Adham and co-workers to describe for the first time in 2012 the detailed technique for a standardized TMpE (17) (Fig. 4).

According to Adham and co-workers, the right side of superior mesenteric artery represents the inferior resection margin of mesopancreas, the origin of celiac trunk represents the posterior resection margin, while the right side of the celiac trunk represents the superior resection margin of mesopancreas (17). Thus, the mesopancreas is considered a triangular flap of tissues (including lymph nodes, lymphatic and nerve plexus, small arteries and veins) that extend from the posterior part of pancreatic head behind the superior mesenteric/portal vein (17).

Furthermore, several other techniques of TMpE were described in the literature (18-21,23,44-47).

Resection of mesopancreas is included in standard pancreatectomy by most pancreatic surgeons (25,48), while others consider it extended lymph nodes dissection (49-51).

A review published in 2013 highlighted the fact that TMpE is not only a matter of lymph

Figure 4. Intraoperative aspects after pancreaticoduodenectomy with total mesopancreas excision (IVC – inferior vena cava; LRV – left renal vein; CT – celiac trunk; CHA – common hepatic artery; PHA – proper hepatic artery; SMA – superior mesenteric artery; SMV – superior mesenteric vein; PV – portal vein; CBD – common bile duct; P – distal pancreas).

nodes dissection but also refers to excision of perivascular neural and soft tissues, including the extrapancreatic nerve plexus (50). Furthermore, TMpE is considered mandatory to minimize the chance of positive resection margins at this level (50,52).

In conclusion, mesopancreas might be a misnomer without precise anatomical boundaries but contains important lymphatic and nervous plexus. Thus, mesopancreas represent a space of utmost importance for resection margins and tumor recurrence in PDAC. Furthermore, TMpE is a real surgical concept that should be standard for any PD for PDAC because it allows increased rates of negative resection margins.

What are the technical refinements developed to facilitate TMpE?

Nakao proposed in 1993 the mesenteric approach in PD to achieve complete resection of the mesopancreas in PDAC (43,53).

Several other technical refinements, grouped as “artery-first” approaches, were proposed to better resect PDAC of the pancreatic head, including TMpE (19-21,45,47,54-59).

Xu and co-workers in a review have shown the potential benefit for improvement of outcomes of “artery-first” PD for PDAC (60). Furthermore, a recent systematic review and meta-analysis has emphasized the reduced loco-regional recurrence rate after “artery-first” approaches for PDAC, compared with standard approach, albeit no significant differences were observed for negative resection margins and overall survivals rates (61).

However, another recent review has shown that there is no clear benefit of “artery-first” approaches to decrease positive resection margins rates or to improve survivals in PDAC (62).

Nevertheless, institutional studies published in 2017 have shown a potential benefit of survival in PDAC with an “artery-first” approach, albeit the statistical significance was not reached (63,64).

In conclusion, “artery-first” approaches appear to facilitate TMpE during PD for PDAC (*Fig. 5*).

Figure 5. Intraoperative aspects of pancreatico-duodenectomy with posterior approach and total mesopancreas excision (Mp – mesopancreas; SMA – superior mesenteric artery)

What is the impact of TMpE on early and long-term outcomes in patients with PDAC?

We have previously highlighted the critical role of TMpE in PDAC (15) and developed it furthermore in clinical practice (65).

Kurosaki and co-workers have found significant differences in overall survivals between patients resected for PDAC with and without TMpE, in favor for patients with TMpE (44). Interestingly, no differences in positive resection margins rates were observed between the groups (44).

Kawabata and co-workers have found significantly increased number of harvested lymph nodes and negative resection margins rates when TMpE was performed (21). Updated data have associated TMpE with significantly less blood loss and decreased loco-regional recurrence rates (66). However, further analyses did not show any significant improvements for overall survivals for both biliary tract cancers (67) and PDAC (68).

Aimoto and co-workers have found significantly more harvested lymph nodes, less blood loss and less local recurrence rates in patients with PD for PDAC and TMpE, compared with standard approach (18).

Perinel and co-workers have found significantly increased number of retrieved lymph

nodes and improved survivals when TMpE was performed (25).

Inoue and co-workers have found significantly less blood loss when TMpE was performed (19). Furthermore, no impact was observed for number of retrieved lymph nodes or positive resection margins rates (69).

Sugiyama and co-workers have found significantly less blood loss when TMpE was performed (46).

Our previous studies have shown significantly less blood loss but no improved survivals with TMpE and posterior approach PD (54).

In summary, the data from the literature regarding outcomes after PD with TMpE for periampullary malignancies have shown negative resection margins rates between 71.6% and 86%, tumor infiltration of the mesopancreas in 23.1% - 82.5% of patients, a median number of harvested lymph nodes between 7.9 and 34, morbidity rates between 33% and 71%, mortality rates between 0% and 5.7%, and median overall survival times between 18.3 months and 20.5 months (17,18, 20,44-46,54,55,68).

At this time, although TMpE appears to be widely considered a key point in resection for PDAC of the pancreatic head (15,20,52), however, it is too early to conclude that it has the same oncological value as total mesorectal excision in rectal cancer (70,71).

A recent study has shown that there are important anatomical differences between the mesorectum and mesopancreas (72):

- a fascia envelops all the structures of mesorectum and allows dissection in an extrafascial plane, which is not the case for mesopancreas;
- the rectal fascia is a landmark for pathology and adequate surgical resection, which is not the case for mesopancreas;
- a circumferential resection margin results from en-bloc resection of the rectum and mesorectum, which is not the case for mesopancreas
- the prognostic impact of circumferential resection margin status can be assessed with respect to the completeness of total

mesorectal excision on the plane of rectal fascia, a situation that cannot be accomplished for mesopancreas that has no anatomic boundaries.

Nevertheless, Verbeke and co-workers have shown that tumor growth is more dispersed in pancreatic head PDAC than in rectal cancer (73).

In conclusion, TMpE with PD for PDAC is feasible and safe and was associated with decreased blood loss, increased number of harvested lymph nodes and negative resection margins rates. However, data about improved survivals in PDAC with TMpE are scarce and, thus, it is too early to conclude that TMpE has the same oncological value as total mesorectal excision in rectal cancer.

Conclusions

Mesopancreas might be a misnomer without precise anatomical boundaries but contains important lymphatic and nervous plexus. Thus, mesopancreas represent a space of utmost importance for resection margins and tumor recurrence in PDAC.

TMpE is a real surgical concept that should be standard for any PD for PDAC because it is safe and feasible, and allows increased number of harvested lymph nodes and increased rates of negative resection margins.

However, data about improved survivals in PDAC with TMpE are scarce and, thus, it is too early to conclude that TMpE has the same oncological value as total mesorectal excision in rectal cancer.

Further studies are urgently needed to draw reliable conclusions.

Funding and conflict of interests: none

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